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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
06/30/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)
	10/593,256	TAVITIAN ET AL.
	Examiner	Art Unit
	TERESA WESSENDORF	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/15/2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *7-36 and 38-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 37 and 45-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☐ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-47 are pending.

Claims 7-36 and 38-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species.

Claims 1-6, 37 and 45-47 are under examination.

Withdrawn Objection/Rejection

In view of the amendments to the disclosure, the objection is withdrawn. Also, the rejection under 35 USC 112, 2nd paragraph is withdrawn in view of the amendments to the claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Rejection-Necessitated by the Amendments

Claims 2 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention.

Claim 2 which recites "pharmaceutically effective affinity for said RPTK" is not supported in the as-filed specification. MPEP 2163.06 clearly states that applicants are to point out where support can be found for the new claim limitations. Also, claim 45 "contiguous" nucleotides of the sequences are not supported in the original disclosure.

Claim Rejections - 35 USC § 112

Claims 1-6, 37 and 45-47 as amended and added, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record as reiterated below.

Applicants are in possession of a method describing Pc12 cells expressing a Ret receptor mutated in the intracellular and extracellular domains and contacting with modified aptamer library of 2-F-py-RNAs. Applicants are not in possession of a method of identifying e.g., aptamers for RPTK wherein the

intracellular and extracellular domain of any cell has been mutated in every conceivable way. The method claims not only enormous cells but also a huge type of mutations intracellularly or extracellularly in the cells. Claim 45 lists Seq. ID. 1 and 2 or a fragment of at least 8 nucleotides of these sequences as the starting nucleic acid combinatorial library but does not define the randomization therein. An adequate written description of a chemical invention requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described."). See

MPEP 2163. One skilled in the art would have been able to make and use the full scope of the claim method drawn to a mutated Ret receptor in PC1 cells through routine experimentation. However Applicants did not describe the invention of claim 1 sufficiently to show they had possession of the claimed genus method using e.g., any aptamers for any RPTK in cells mutated intra and extracellularly. See, e.g., Noelle V. Lederman, 355 F.3D 1343, 96 USPQ2dI508, 1513 (Fed. Cir 2004) ("invention is, for purposes of the 'written description' inquire, whatever is now clamed"). Applicants have disclosed only 2-F-Py-RNA aptamer as the mixture of nucleic acids and cells expressing Ret mutated at a single location, e.g., intracellularly (RetM198T). Therefore, the skilled artisan cannot envision all the contemplated aptamers, cells and RPTK possibilities recited in the instant claim method. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See Fiefs v. Revel, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.II2, ¶1 "Written Description" Requirement make clear that the written description

requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column). Vas-Cath Inc. v. Mahurkar, 19 USPQ2d iiii, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116. Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398. Applicants are directed to the final Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, [1

"Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Response to Arguments

Applicants argue that it was well within the skill of those in the art, which is generally recognized as post-doctoral level, to practice the method of the invention with other cell types, other mutated RPTK and other starting mixtures of nucleic acids. Mutations in tyrosine kinase receptor proteins could have been easily localized to the intracellular or extracellular domains using conventional techniques and it would have been well within the skill of the art to identify cells not expressing tyrosine kinase receptors or such receptors in inactive form. The attached references--Ohuchi, et al. (2006) and Chen, et al. (2009) show that one of skill in the art would have been enabled to easily implement the claimed method for other cell types, other kinds of RPTK receptor proteins, and other starting mixtures of nucleic acid sequences. Ohuchi, et al. teaches obtaining RNA aptamers recognizing transforming growth factor-β type III receptor. (i.e., a RPTK different from Ret) expressed by Chinese hamster ovary cells, see the abstract. Moreover, Ohuchi, et al. related their method to that of the invention at page 7, right col. (at the end of the paragraph before the Acknowledgments):

> Following the completion of all experiments described here, we became aware of a recent study that reported the isolation of RNA aptamers against human receptor tyrosine kinase RET using RET-expressing cells as targets in a modified SELEX procedure similar to TECS-SLEX [15]i.

Chen, et al. teach obtaining single-stranded DNA (ssDNA) aptamers recognizing the HCV E2 envelop glycoprotein expressed by CT26 cells from a starting mixture of ssDNA, see page 2, the paragraph bridging the left and right columns, thereby showing that such a method can be extended to targets even beyond the RPTKs to all types of cells capable of expressing the target and to starting nucleic acid mixtures different from 2'-flouropyrimidine RNAs.

In reply, skilled in the art are at post-doctoral level however, the high unpredictability in the art is one that said skilled in the art cannot reliably predict. The newly presented art, e.g., Ohuchi evidences such. Ohuchi teaches specific cells, CHO, expressing human transforming growth factor-β type III receptor and no other species or indication that the method specific for said species apply to all types or kinds of receptors and/or cells. Ohuchi became aware of applicants' work only after the completion of their work i.e., did not apply applicants method to their work. Even assuming this is valid, which is not since different experimental conditions have been

specifically applied for each species. The two species could not be considered representative of the huge scope of the genus claim, absent any indication in the specification or Ohuchi et al. In fact Ohuchi teaches at page 6, bridging col. 1 and col.2:

> To confirm the specificity of aptamer A07, SPR analysis was also carried out using...recombinant TGF- type I and type II receptors (TbRI and TbRII), as well as endoglin, a homolog of the extracellular domain of TbRIII. **In all cases, no binding signal was observed** (data not shown). **Unexpectedly,** the addition of a small amount of aptamer A07 increased the amount of complex formation (Fig. 6, lane 2). Since the addition of N60 RNA also enhanced complex formation (Fig. 6, lane 7), this result is probably due to non-specific effects such as neutralization of charge repulsion between the proteins or capture of certain buffer components, and not due to specific interaction between the aptamer and protein. Complex formation was reduced proportionately with the addition of…aptamer A07 (Fig. 6, lanes 2 and 4), while...N60 (random) RNA did not inhibit the binding (Fig. 6, lane 7). These results suggest that aptamer A07 is inhibitory to the association of TGF- with TbRIII (page 7, col. 1).

It is also known in the art that RTKs elevated expression levels are likely to be engaged in a broader range of interactions. Applicants' instant remarks below that "the usual feeble expression rate of membrane proteins by cells modified to express a membrane protein that too few putative aptamers would have been selected at each round of selection to yield a true aptamer specifically binding to the target" lend support to the unexpected observations or findings of Ohuchi.

There are just too numerous unexpected parameters and/or conditions to lead one skilled in the art to the claim genus method given only the two argued species employed in the method.

The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure indicates that the applicants have invented species sufficient to constitute the gen[us]. Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

The written description requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed." Capon v. Eshhar, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005). Further, the written description requirement **promotes the progress of the useful arts by ensuring that** patentees adequately describe their inventions in their patent specifications in exchange for the right to exclude others from practicing the invention for the duration of the patent's term. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient

detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116. See MPEP 2163.

New Claim Rejection – Necessitated by Amendments

35 USC § 112, second paragraph

Claims 2 and new 45-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 2 is vague and indefinite as to what would constitute a "**pharmaceutically effective** affinity for RPTK", within the claim context, especially in the absence of positive support or definition in the specification.

2. Claim 45 is vague and indefinite as to the metes and bounds of the claim "contiguous" nucleotides of either Seq. ID. 1 or 2, especially in the absence of positive support or definition in the specification. It is vague and indefinite as to which 8 contiguous residues are being referred to in either Seq. ID 1 or 2.

Claim Rejections - 35 USC § 103

Claims 1-6, 37 and 45, as amended and new claims 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (PNAS, 8/2003) in view of Yayon et al (USP 7498416) for reasons of record as reiterated below.

Chen et al discloses at e.g., page 9226, col. 2; a method of identifying RNA aptamers against RTKs. Libraries of randomized RNAs is screened in vitro using SELEX. RNA aptamers used can be with fluorine in the 2' position which significantly enhances the half-life of RNA aptamers in serum. Aptamers have been selected successfully against several extracellular protein ligands, such as vascular endothelial growth factor (VEGF). As a target for aptamer selection, RTKs stand out through their large size. Chen has successfully selected RNA aptamers against the ECD of HER3 and evaluated one aptamer in particular to demonstrate its potential for the analysis of RTK interactions and its potential use as an inhibitor against cancer cells.

Chen discloses at page 9227, col. 1 up to page 9230, col. 2 the method as comprising producing single-stranded DNA templates for SELEX that includes contiguous randomized positions flanked by constant regions (Fig. 1). The constant regions included

targets for PCR primers and cloning sites and a promoter. A filter binding assay was used for the first eight rounds of selection. The RNA pool was first counterselected by passing through a filter. The counterselected RNAs were then incubated with HER3ECD. Over the course of selection the ratio of protein to RNA was gradually lowered from 4:1 to 1:2. Unbound aptamers were separated from protein-bound aptamers. A gel-shift assay was used in the last seven rounds of selection. RNA was incubated with HER3ECD as described above. Gel electrophoresis was carried out. The retarded band was isolated, and RNA was extracted from the gel in elution buffer. For both selection methods, the RNA was subsequently reverse-transcribed into cDNA Finally, the cDNA was PCR-amplified for the next round of selection. The bound and unbound aptamer was measured and identified. Chen does not teach that the tyrosine kinase receptor, HER3 is mutated at the extracellular and intracellular region. However, Yayon discloses at e.g., col.24, line 35+; that other screens can be carried out on cell lines expressing a RPTK carrying a mutation, such as the FDCP-FR3 each line expressing the FGFR3 achondroplasia mutation. The receptors of this line become constitutively active, e.g. are able to signal in the absence of a ligand as determined by ERK (MAPK) phosphorylation, a downstream effector. Ret receptor is disclosed by Yayon at

e.g., col. 19, line 60. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to mutate the tyrosine kinase receptor of Chen in the manner taught by Yayon. One would have a reasonable expectation of success since its counterpart, the unmutated part has been successfully screened by Chen using SELEX method. One would be motivated to mutate the receptor as it becomes constitutively active, e.g. are able to signal in the absence of a ligand as determined by ERK (MAPK) phosphorylation, a downstream effector as taught by Yayon.

Response to Arguments

Applicants state that Yayon are primarily directed to antibodies or antibody fragments against the extracellular domain of FGFR3 and involve applying an antibody selection method, that is, using a dimeric soluble form of FGFR3 to the soluble extracellular domains of an RPTK, such as Ret, see col. 7, lines 10-19 and col. 10, lines 44-60. Yayon further suggest that antibodies could be screened with cell lines expressing a mutated RPTK, such as the FDCP-FR3 each cell line, see col. 24, lines 55-60. One of ordinary skill in the art at the time of invention would have not looked to or considered its antibody-related teachings with respect to methods for screening aptamers

from a starting mixture of nucleic acids. To emphasize this difference the present claims have been directed to aptamers and omit the term "ligands". Moreover, neither Chen, nor Yayon provided any motivation for screening aptamers against RPTKs expressed by cells. Yayon teaches away from this because it expressly indicates that the target for screening antibodies against Ret should be a soluble extracellular domain of Ret.

In reply, Yayon is employed not for the purpose as argued. Rather for its teachings of intracellular and extracellular mutations. Chen is the one that teaches the method of aptamer selection. Nonetheless as known in the art aptamers, very similar to antibodies, have high affinity and specificity to target molecules. The unique qualities of aptamers such as the absence of immunogenicity, little or no toxicity and robust against both reducing conditions and heat denaturation would motivate one to replace antibodies with aptamers.

Applicants cannot show non-obviousness by attacking the references individually where the rejection is based on a combination of references. In re Young, 159 USPQ 725 (CCPA 1968).

When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or **a different one**. If a person of ordinary skill can implement a predictable variation, § 103

likely bars its patentability. Here, Yayon suggests applicability to RTYK and not only to antibodies.

Applicants state that one of ordinary skill in the art would not have had a reasonable expectation of success for successfully implementing a method for selecting aptamers specifically directed to a RPTK by using cells modified to express RPTK since the prior art did not show that specific aptamers could in fact be screened using cells modified to express a membrane protein of any type. Indeed, one of ordinary skill in the art would have expected that in view of the usual feeble expression rate of membrane proteins by cells modified to express a membrane protein that too few putative aptamers would have been selected at each round of selection to yield a true aptamer specifically binding to the target.

In reply, absolute predictability is not a prerequisite for obviousness. In re Konig 190 USPQ 425 (CCPA 1976). The feeble expression rate of membrane proteins by cells is immaterial as much as the combined teachings of the prior art teaches all the elements of the claim method.

Allowable Subject Matter

Newly presented claim 46 would be allowable if rewritten or amended to include the limitation of claims 47 and 45 (upon

overcoming the rejection under 35 U.S.C. 112, 2nd paragraph, set forth above).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims 7-36 and 38-44 drawn to an invention nonelected invention. A complete reply to the final

rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marchel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/
Primary Examiner
Art Unit 1639